been amended. Support for the amendments can be found throughout the specification. Further, new claims 25-50 have been added. Support for the new claims can also be found through the specification. Accordingly, no new matter has been added.

The IRES function and encapsidation properties of the nucleotide sequence of the invention as originally defined in previous claim 1 are the subject matter of two series of claims, claims 25-30 directed to the IRES function and claims 31-36 directed to the encapsidation properties.

New claim 25 recites a method for providing an internal ribosome entry site (IRES) to a vector for the transfer and expression of one or more genes of interest comprising the step of introducing into said vector a nucleotide sequence isolated from the 5' end of the genomic RNA of a type C retrovirus selected from the group consisting of REV and MSV or from the DNA equivalent of said genomic RNA. The claim is supported by previous claim 1 (providing an internal ribosome entry site (IRES) to a vector by using a nucleotide sequence isolated from the 5' end of the genomic RNA of a type C retrovirus), claim 2 (selected from the group consisting of REV and MSV) and page 5, lines 30-31 of the specification (or from the DNA equivalent of said genomic RNA). Dependent claims 26-30 recite the characteristics as defined by the canceled claims 4, 5, 6 and 7.

Kindly note that new claim 28 has been further amended compared to the previous claim 5 by specifying that the nucleotide sequence comprises at least 100 nucleotides and at most 800 nucleotides substantially homologous or identical to the sequence of SEQ ID NO:1. Support for this amendment can be found on page 7, lines 20-27 of the specification

and has been introduced in response to the clarity objection raised with respect to the expression "all or part of the specified sequence."

New claim 31 recites a method for allowing or activating the encapsulation of a retrovirus or a retroviral vector, comprising the step of introducing into said retrovirus or retroviral vector, a nucleotide sequence isolated from the 5' end of the genomic RNA of a type C retrovirus selected from the group consisting of REV and MSV or from the DNA equivalent of said genomic. Support for claim 31 can be found on page 5, lines 38-39 of the specification (activating the encapsulation of a retrovirus or a retroviral vector), by previous claim 1 (a nucleotide sequence isolated from the 5' end of the genomic RNA of a type C retrovirus), previous claim 2 (selected from the (group consisting of REV and MSV) and page 5, lines 30-31 of the specification (or from the DNA equivalent of said genomic RNA). Dependent claims 32-36 recite the characteristics as defined by the canceled claims 4, 5, 6 and 7 have been added. New claim 34 reciting the essential characteristics of the previous claim 5 has been amended as discussed above.

New claim 37 is directed to a method of treating or preventing a genetic disease, a cancer or an infection disease, comprising the step of administering a therapeutically effective quantity of a vector, a viral particle or a cell of the invention to a patient requiring such a treatment. Support for claim 37 can be found on page 19, lines 24-29 of the specification.

New claim 38 recites a method for the preparation of one or more polypeptides of interest by the recombination route, comprising the step of culturing in vitro a cell comprising a vector of the invention or infected with a viral particle of the invention and

harvesting said polypeptide(s) from the supernatant or from the cell culture. Support for claim 38 can be found on page 18, lines 10-13 of the specification and previous claim 21. The production of transgenic animals as found in originally filed claim 21 is now the subject matter of new claim 39, which recites a method for producing a transgenic animal comprising the step of integrating into the genome of said animals a vector according to the invention (supported by page 18, lines 14-18 of the specification and previous claim 21).

New claim 40 recites a method for expressing one or more genes of interest in pluripotent cells comprising the step of transfecting or infecting said pluripotent cells with a vector of the invention, a viral particle generated from a viral vector of the invention or a pharmaceutical composition prepared from said vector or viral particle. Support for claim 40 can be found on page 20, lines 1-4 of the specification and in previous claim 24. Dependent claim 41 specifies the central nervous system origin of the pluripotent cells, and support for this claim can be found on page 20, line 5 of the specification and in previous claim 24.

As discussed below, the modifications proposed in these new claims take into consideration the enablement objections raised under 35 U.S.C. § 112, first paragraph, the clarifications requested under 35 U.S.C. § 112, second paragraph, and the objections expressed under 35 U.S.C. § 102 and 35 U.S.C. § 103.

## I. Rejections under 35 U.S.C. § 101

Claims 1-7, 20, 21 and 24 have been rejected under 35 U.S.C. § 101. The Examiner has stated that the claimed recitation of a use, without setting forth any steps

involved in the process results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. § 101. This rejection is rendered moot in light of the cancellation of claims 1-7, 20, 21 and 24.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 1-7, 20, 21 and 24 under 35 U.S.C. § 101.

## II. Rejections under 35 U.S.C. § 112, first paragraph

*Enablement*

Claims 20, 22 and 23 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification is such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. Specifically, the Examiner has stated that the specification does not enable for the intended use of the claimed pharmaceutical composition and method for preparing the same, because at the effective filing date of the instant application, the art of gene therapy was immature and highly unpredictable. Applicants respectfully traverse this rejection.

The present specification provides more than an adequate disclosure to permit one of ordinary skill in the art to practice the present invention. As recognized by the Examiner, the specification discloses the construction of mono and dicistronic vectors comprising the 5' untranslated (5'UT) region of an avian reticuloendotheliosis virus of type A (REV-A). Two types of vectors have been constructed and derived, respectively, from plasmids (see example 1) and retroviral vectors (see example 2). The working examples

demonstrate the capacity of the 5'UT REV-A sequence to allow the re-initiation of the translation in a 3' cistron (IRES function) and direct the synthesis of the cistron-encoded product and to enhance the encapsidation of retroviral RNAs. Once a REV A-containing vector is made, the specification discloses the introduction of such a vector into complementation cells (see example 2.2), the collection of virions obtained from the complementation cells (see example 2.2), the introduction of those virions into recipient cells of neuroectodermal origin (see example 3) and demonstrates the production of the gene products in the recipient cells both in a non-differentiated and a differentiated state (see example 3). These results prove that the IRES function of the REV A sequence is independent of the molecular events that go with cell differentiation.

The working examples have been conducted with the reporter genes plap (placental alkaline phosphatase) and neo which are representative examples of any gene of interest. Applicants submit that other genes of interest (e.g. therapeutic genes) can be used in place of the plap and neo genes. Methodologies for the isolation of a particular gene, for its cloning into a vector and for introduction of the vector into an animal or human host were well known to the art prior to the effective date of the present application. Such methods are for example described in the gene therapy patent U.S. Patent No. 5,399,346 issued on March 21, 1995 as well as in the various RAC protocols that have been published in *Human Gene Therapy* before the effective filing date of the present application.

The Examiner also asserts that the specification does not enable for the intended use of a pharmaceutical composition and of a method of gene therapy, because at the effective filing date of the subject application, the art of gene therapy was immature and highly

unpredictable. To support his argument, the Examiner quotes from a number of articles which reviewed the state of the art of gene therapy and, in particular, Dang et al. which summarized a workshop held in March 1998 which was devoted to recent advances in cancer gene therapy. To introduce this subject matter, Dang et al. noted, as pointed out by the Examiner, that "further advancement in all fields including gene delivery, gene expression, immune manipulation and the development of molecular targets is needed to make gene therapy a reality." He further cites the conclusion of a committee of experts which found that "human gene therapy is an immature science with limited understanding of gene regulation and disease models for preclinical studies." Nevertheless, Dang et al. reviewed several studies of convincing gene transfer and expression obtained with viral vectors or engineered cells. For example, in the Dang et al. publication, Dr. Verma reported the substantial progress that has been obtained with lentivirus-based vectors, that are believed to circumvent most of the actual limitations observed with the standard vectors. In particular, lentivirus-based vectors are able to transduce genes into cells independently of their growth status (quiescent or proliferative) and show no evidence of host immune responses (Dang et al., last paragraph of p. 471, second column and first sentence p. 472 first column). Further, Dr. Cowan conducted two clinical trials of retroviral-mediated transfer of the multidrug resistance gene MDR1 into PBPC (peripheral blood progenitor cells) and CD34+ cells. These trials demonstrated evidence of in vivo selection of MDR1-expressing cells, which allow these patients to under go intensive chemotherapy cycles (Dang et al., first and second paragraph p. 472 first column). Dr. Kohn disclosed improved retroviral vectors modified in the cis-acting elements allowing

high expression levels and transduction of embryonic cells (Dang et al., second paragraph p. 472 second column). Finally, Dr. Lattime reported encouraging phase I clinical studies conducted with a vaccinia virus expressing GM-CSF gene. The therapeutic cyclic was found to be expressed both early and late in the treatment course. Regression of injected tumoral lesions was observed as well as of distant uninjected lesions in a certain number of patients, suggesting the development of a systemic antitumor immunity. Dang et al. concluded that "there was a unique level of enthusiasm that many of the obstacles could be overcome with meticulously designed basic and clinical studies." (Dang et al., last sentence p. 474).

Moreover, encouraging clinical data have been reported during the years of 1999-2000 as documented in the enclosed publications discussed below. Gene therapy has achieved success in four early stage clinical trials, differing by the type of delivery vectors, therapeutic genes, routes of administration and applications used in each study:

-Kay et al. (Nature genetics 24:257-61, 2000) reported clinical study of intramuscular injection of an AAV vector expressing human Factor IX in three adults with severe hemophilia B. This approach appeared to be safe and showed evidence of Factor IX gene expression. Notably, one of the patients in a low-dose cohort showed detectable circulating levels of Factor IX above 1%, allowing the reduction of his need for conventional Factor IX concentrate. A reduction of bleeding episodes was also observed in another patient.

-In the study of Isner et al. (J. Clin. Invest. 103:1231-6, 1999), naked DNA encoding the angiogenic growth factor VEGF was injected into the skeletal muscles

of patients with critical limb ischemia resulting from an inadequate blood supply. A noticeable and long-lasting benefit was observed in a large proportion of patients including those who would otherwise have faced amputation.

-Khuri et al. (Nature Medicine, 6:879-85, 2000) studied the effect of an intratumoral injection of a p53-encoding adenovirus (ONYX-015) in combination with standard chemotherapy. The combined therapy was well tolerated and did not induce significant levels of toxicity. The treatment caused an objective response (at least 50% reduction in tumor size) in 63% of patients, including 27% complete responses. None of the tumors that demonstrated an objective response had progressed after a mean follow up of 6 months, whereas all non-injected tumors treated with chemotherapy alone had progressed.

-Cavazzana-Calvo et al. (Science 288:669-72, 2000) reported a gene therapy trial for severe combined immunodeficiency based on ex vivo infection of progenitor CD34+ cells with a retroviral vector encoding a functional γc gene (which is defective in SCID children). Ten months after transduced CD34+ cells re-implantation, T and NK cells expressing the transferred γc gene were detected and immune functions, including antigen-specific responses, were comparable to those of normal children. Thus, gene therapy without any palliative treatment was able to provide full correction of SCID disease, allowing the treated children to leave the protective isolation and enjoy normal life.

From the above, it can be concluded that substantial improvements in gene transfer technology have been obtained and that clinical benefits from gene therapy have been clearly demonstrated with a variety of vectors, therapeutic genes, administration routes and applications.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 20, 22 and 23 under 35 U.S.C. § 112, first paragraph.

Claims 1-18 have been rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a mono- or dicistronic vector for the expression of one or more genes of interest comprising a nucleotide sequence derived from all or part of the 5' end of the genomic RNA of a type C retrovirus selected from the group consisting of REV, MSV, FMLV and MoLV, wherein said nucleotide sequence acts as an entry site in a vector and for encapsidation of a retroviral vector, a viral particle generated from the same vector and a method of incorporating said nucleotide sequence into the mono- or dicistronic vector, allegedly does not reasonably provide enablement for any and all polycistronic vectors for the expression of one or more genes of interest comprising a nucleotide sequence derived from all or part of the 5' end of the genomic RNA of any and all type C retrovirus, wherein said nucleotide sequence acts as an internal ribosomal entry site and for encapsidation of a retroviral vector, a viral particle generated from said polycistronic vector and a method for incorporating said nucleotide sequence into the polycistronic vector. Further, the Examiner has stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use

the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

The Examiner has further commented on the results obtained with retroviral vectors of the present invention comprising a REV A nucleotide sequence acting as an IRES and subsequently published by the inventors in Lopez-Lastra (Human Gene Therapy 8:1855, Nov. 1997). The Examiner has noted the reduced viral titers obtained with the retroviral vectors including both a VL30-derived encapsidation region and a REV A-derived IRES sequence (such as pREV-HW2), which are explained by a selective interaction between the REV A and the VL30 sequences located in the same transcriptional unit.

Applicants submit that the retroviral vectors comprising both VL30 sequences acting for encapsidation and REV A sequences acting as an IRES are sufficiently functional to allow co-expression of genes of interest (transient expression data and translational rate are comparable to those obtained with the control vector). It is noted that the retroviral vectors combining both a MoLV-based encapsidation region and a REV A-derived IRES (such as pRVHW3) are unexpectedly highly performing in terms of viral titers and expression levels compared to the conventional vectors.

In order to expedite prosecution and not acquiesce to the Examiner's rejection, Applicants have restricted the scope of the claims to a vector comprising a nucleotide sequence isolated from the 5' end of the genomic RNA of a REV or MSV retrovirus, for which enablement is established and recognized by the Examiner. However, we may consider later on the filing of a continuing application based on the deleted subject matter.

Therefore, claim 8 has been amended to recite "a vector for the expression of one or more genes of interest comprising a nucleotide sequence isolated from the 5' end of the genomic RNA of a type C retrovirus selected from the group consisting of REV and MSV or from the DNA equivalent of said genomic RNA." Support for this amendment can be found in previous claim 1 (nucleotide sequence isolated from the 5' end of the genomic RNA of a type C retrovirus), in previous claim 2 (selected from the group consisting of REV and MSV), and on page 5, lines 29-31 of the specification (or from the DNA equivalent of said genomic RNA). Please note that 5 dependent new claims have been added (claims 42-46) that recite the characteristics defined in previous claims 4-7. Moreover, a new claim (claim 47) has been added to cover the unexpectedly efficient retroviral vector comprising a MoMLV encapsulation region and a REV A IRES.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 1-18 under 35 U.S.C. § 112, first paragraph.

Claim 21 has been rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of preparing one or more polypeptides of interest *in vitro* using a mono- or dicistronic vector comprising a nucleotide sequence derived from all or part of the 5' end of the genomic RNA of a type C retrovirus selected from the group consisting of REV, MSV, FMLV and MoLV, a viral particle generated from a viral vector comprising the same features or a cell comprising said vector or said viral vector, allegedly does not reasonably provide enablement for a method of preparing one or more polypeptides of interest by any and all recombinant routes, or a method for the production of a transgenic animal using a vector of claim 8, a viral particle generated from

a viral vector of claim 8 or a cell comprising the same vector or viral particle. Further, the Examiner has stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

This rejection is rendered moot in light of the cancellation of claim 21. However, to the extent that this rejection may apply to claims 25-50, it is respectfully traversed. New claim 38 recites a method for the preparation of one or more polypeptides of interest by the recombination route, by culturing in vitro a cell comprising a vector as claimed in amended claim 8 or infected by a viral particle having the same features. As recognized by the Examiner, the specification is enabling for such a method.

Moreover, the Examiner states that the specification is not enabled for a method for the production of a transgenic animal using a vector, a viral particle or a cell of the invention as claimed in the previous claim 21. In particular, the Examiner alleges that the state of the art for transgenics was highly unpredictable at the effective filing date of the present application and the Examiner bases his arguments on publications by Mullins et al. (1996), Seamark (1994) and Wall (1996).

However, Applicants respectfully disagree and stress to the Examiner the successful transgenics experiments reported in these publications. For example, in Mullins et al. (p. S38) it is stated that:

-The human apolipoprotein A-1 gene was successfully expressed in the rat, resulting in increased serum HDL cholesterol concentration and attempts to therapeutically

lower apo B100, and hence LDL and lipoprotein concentrations, in the rabbit were successful.

-The rabbit has also been used in HIV-1 research with the development of a line expressing the human CD4 protein on T lymphocytes. Susceptibility to HIV was demonstrated.

-A more successful application of transgenesis in farm animals has been the production of biomedically important proteins. Transgenic swine expressing high levels of human hemoglobin were generated using the locus control region from the b-globin gene cluster.

-The BLG promoter was used to direct expression of human alpha 1 antitrypsin in lines of transgenic mice and sheep.

-High levels of expression of human tissue plasminogen activator were obtained in goat's milk under the control of the goat b-casein promoter.

Applicants further submit that a large number of patents covering transgenic animals were issued well before the priority date of the present application (e.g., U.S. Patent No. 5,175,383; U.S. Patent No. 4,736,866; and U.S. Patent No. 5,175,384).

Thus, even if improvement of the technology remains to be made, the examples provided in the publications cited by the Examiner and the state of the art establish that transgenesis had a reasonable expectation of success in a wide variety of species at the effective filing date of the present application. It is well settled law that Applicants need not to teach, and preferably omit, that which is well known in the art. Section 112, first paragraph, requires no more than a disclosure to enable the skilled artisan to practice the

invention commensurate with the scope of the claims and, Applicants submit that this requirement has clearly been met with regard to the production of transgenic animals as claimed by the new claim 39.

Therefore, Applicants respectfully request withdrawal of the rejection of claim 21 under 35 U.S.C. § 112, first paragraph.

Claim 24 has been rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of transfection or infection of pluripotent cells *in vitro* using a mono- or dicistronic vector comprising a nucleotide sequence derived from all or part of the 5' end of the genomic RNA of a type C retrovirus selected from the group consisting of REV, MSV, FMLV and MoLV, a viral particle generated from a viral vector comprising the same features, allegedly does not reasonably provide enablement for the same method *in vivo* or the use of a pharmaceutical composition comprising a vector of claim 8 or a viral particle generated from a viral vector of claim 8 in the same method. Further, the Examiner has stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

The specification provides evidence that the vectors of the present invention are effective transducers of human multipotent neural precursor cells (30-50% of transduced cells as indicated; page 34, line 38 and page 35, line 4 of the specification), contrary to conventional retroviral vectors (page 35, lines 1-2 of the specification). The REV A-containing vectors maintain co-expression of two genes of interest after the induction of

neural differentiation. All together, these data establish that the vector of the present invention can provide an acceptable means of ensuring the stable and long-term translation of two gene products in human neural precursor cells and in their differentiated progeny.

As discussed on page 1130, first column, of Derrington et al. (Human gene Therapy 10:1129-38, 1999, attached hereto), it was known in 1992-1995 that neural precursor cells can be isolated, expanded in vitro and grafted back into the brains of host animals with their neuronal and glial progeny developing appropriately in the host brains. The authors indicated that "the capacity of CNS-derived multipotent precursors to integrate functionally within a host brain suggests that transplantation of neural precursor cells that have been genetically engineered to produce molecules of therapeutic potential may provide a long term strategy to modulate the consequences of neurogenetic diseases or neural degeneration in the brain."

Thus, these data provide evidence that a method for expressing in vivo one or more genes of interest into pluripotent cells by transfecting or infecting said pluripotent cells with a vector or a viral particle according to the invention or a pharmaceutical composition prepared from said vector or viral particle, as claimed now in the new claim 40, would be effective and the present specification provides more than an adequate description so as to permit the practice of the claimed method by one of ordinary skill in the art.

Therefore, Applicants respectfully request withdrawal of the rejection of claim 24 under 35 U.S.C. § 112, first paragraph.

*Written description*

Claims 1, 2 and 8-24 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

The proposed new set of claims is restricted to products and methods employing a nucleotide sequence isolated from REV or MSV retrovirus and, therefore, should overcome this objection.

The examiner has further stated that the specification falls to provide sufficient information regarding the construction of a polycistronic vector comprising at least three genes of interest and that it would have required a skilled artisan undue experimentation to attain a polycistronic vector efficient for the expression of the three genes of interest.

Applicants respectfully disagree and indicate that the teaching of suitable genes of interest is provided on pages 13-14 of the specification and suitable internal promoters are provided on page 14, line 33 to page 16, line 6. Moreover, an exemplary structure of a polycistronic vector expressing three genes of interest is illustrated on page 11, lines 5-20, with the indication that it is preferable that the expression cassette directed by the internal promoter be in an opposite orientation relative to the retroviral LTRs.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 1, 2 and 8-24 under 35 U.S.C. § 112, first paragraph.

## III. Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-24 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicants respectfully traverse this rejection.

Claim 1 has been rejected because the term "and/or" is allegedly unclear and renders the claim indefinite. Claim 1 has also been rejected because the term "improving" is a relative term which is not defined by the claim. The Examiner has stated that the specification does not provide a standard for ascertaining the requisite degree of improvement. Further, claim 1 has been rejected for allegedly being indefinite for reciting a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation. This rejection is rendered moot in light of the cancellation of claim 1.

Claim 4 has been rejected for allegedly being indefinite for reciting a broad range or limitation (a genomic RNA of an avian reticuloendotheliosis virus) followed by a narrow range or limitation (in particular of type A) within the same claim. This rejection is rendered moot in light of the cancellation of claim 4.

Claims 1 and 3-5 have been rejected for allegedly being indefinite for reciting the phrase "part of." The Examiner has stated that the metes and bounds of the claim can not be determined because of the ambiguity of such a phrase. This rejection is rendered moot in light of the cancellation of claims 1 and 3-5. However, to the extent that this rejection may apply to claims 25-50, it is respectfully traversed.

The new claims 25-27 and 31-33 recite that the nucleotide sequence is isolated from the 5' end of the specified type C retrovirus genomic RNA (support can be found on page 6, line 9). The new claims 28 and 34 specify that the nucleotide sequence comprises at least 100 nucleotides and at most 800 nucleotides substantially homologous or identical to the sequence of SEQ ID NO:1 (support may be found in previous claim 5 and on page 7, lines 20-27 of the specification).

Claim 9 has been rejected for reciting the phrase "characterized in." The Examiner is not clear as to what other characteristics the claimed vector comprises or does not comprise. Further, claim 9 has been rejected for not reciting proper Markush language. This rejection is rendered moot in light of the amendment to claim 9. Specifically, claim 9 has been amended to recite "wherein said vector" instead of "characterized in that it" and claim 9 has been amended to recite the proper Markush language.

Claim 10 has been rejected for reciting the term "and/or." The Examiner is not clear if the nucleotide sequence is used to improve the encapsidation of the vector or if the nucleotide sequence is used as an IRES site. Further, claim 10 has been rejected for reciting the term "improving." This rejection is rendered moot in light of the amendment to claim 10.

Claim 12 has been rejected for reciting the term "optionally." The Examiner is not clear if the claimed retroviral vector contains the elements stated in step (c) or not. This rejection is rendered moot in light of the amendment to claim 12.

Claim 14 has been rejected for reciting a broad range or limitation (a murine retrovirus) followed by a narrow range or limitation (especially from an MoMLV) within

the same claim. This rejection is rendered moot in light of the amendment to claim 14. Specifically, claim 14 has been amended to no longer recite "especially from a MoMLV."

Claims 15-18 have been rejected for reciting a broad range or limitation followed by a narrow range or limitation within the same claim. The Examiner has stated that claim 15 recites a broad range starting at 265 and ending at 578 followed by a narrow range starting from 452 and ending with 578. The Examiner has further stated that in claim 16, the broad recitation of "an REV virus" is followed by the narrow recitation of "especially SNV, and the broad range starting from nucleotide 1 and ending with nucleotide 578 is followed by the narrow range starting from nucleotide 265 and ending with nucleotide 578. With regard to claim 17, the Examiner has stated that the claim recites the broad term "interleukin (IL)" followed by the narrow recitation of "especially IL-2." This rejection is rendered moot in light of the amendments to claims 15-18.

Claims 23 and 24 have been rejected for reciting a broad range or limitation followed by a narrow range or limitation within the same claim. Specifically, the Examiner has stated that claim 23 recites the broad range of "$10^4$ and $10^{14}$ pfu" followed by the narrow range of "$10^6$ and $10^{11}$ pfu," and claim 24 recites the broad term "pluripotent cells" followed by the narrow recitation of "especially pluripotent cells of the central nervous system." This rejection is rendered moot in light of the amendments to claim 23 and the cancellation of claim 24.

Claim 20 has been rejected for reciting "and/or." The Examiner is not clear as to whether the preparation is used for the treatment or the prevention or both. This rejection is rendered moot in light of the cancellation of claim 20.

Claim 21 has been rejected because the phrase "for the protection of a transgenic animal" is unclear to the Examiner. The Examiner believes Applicants intend the phrase "for the production of a transgenic animal." This rejection is rendered moot in light of the cancellation of claim 21.

Claims 1-7, 20, 21 and 24 have been rejected because the claims provide for a use but the claims do not set forth any steps involved in the method or process. The Examiner has stated that it is unclear what method Applicants are intending to encompass. This rejection is rendered moot in light of the cancellation of claims 1-7, 20, 21 and 24.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 1-24 under 35 U.S.C. § 112, second paragraph.

## IV. Rejections under 35 U.S.C. § 102

Claims 1, 2, 8-10, 12, 18, 19 and 22 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Berlioz et al. (*J. Virol.* 69: 6400-7 (1995)). The Examiner has stated that Berlioz et al. discloses a preparation of monocistronic and dicistronic plasmid DNA constructs comprising the rat VL30 region of the Harvey murine sarcoma virus leader, and demonstrated that the rat VL30 region serves as an IRES site and efficiently directs the expression of a 3' cistron *in vitro* and *in vivo*. The Examiner has further stated that Berlioz et al. also discloses the construction of a dicistronic MLV-derived retroviral vector, pVL-CBT2, comprising the VL30 sequence inserted between phosphate and neomycin genes. This rejection is rendered moot in light of the cancellation

of claims 1 and 2. However, to the extent that this rejection may apply to remaining claims 8-10, 12, 18, 19 and 22, it is respectfully traversed.

Berlioz et al. describes polycistronic vectors comprising the rat VL30 region acting as an IRES to direct the expression of a 3' cistron in vitro and in vivo. The examiner bases his argument on the fact that this VL30 region was isolated from the 5' end of the Harvey murine sarcoma virus which belongs to the type C retrovirus family.

As discussed above, the scope of the claims has been restricted to the use of a nucleotide sequence isolated from the 5' end of the genomic RNA of a REV or MSV virus. This limitation renders the claimed invention novel over Berlioz et al.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 1, 2, 8-10, 12, 18, 19 and 22 under 35 U.S.C. § 102(b).

Claim 22 has been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Hora et al. (U.S. Patent No. 5,997,856). The Examiner has stated that Hora et al. discloses an aqueous composition comprising an IL-2 polypeptide and that the IL-2 polypeptide is in an aqueous composition that is suitable as a pharmaceutical vehicle. This document describes a composition comprising an IL-2 polypeptide prepared from a retroviral vector. This rejection is rendered moot in light of the amendment to claim 20. Specifically, claim 22 has been amended to delete this feature from the claimed composition.

Therefore, Applicants respectfully request withdrawal of the rejection of claim 22 under 35 U.S.C. § 102(e).

## V. Rejections under 35 U.S.C. § 103

Claims 1, 2, 8-12, 17-19, 21-23 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Berlioz et al. (U.S. Patent No. 5,925,565) in view of Berlioz et al. (*J. Virol.* 69: 6400-7 (1995)). The Examiner has stated that Berlioz et al. (U.S. Patent No. 5,925,565) discloses a viral particle, an isolated cell comprising the recombinant vector or viral particle, and a method for incorporating a DNA encoding a protein of interest into a cell *in vitro*, that Berlioz et al. discloses most of the limitations of the claims. Further, the Examiner has stated that Berlioz et al. (*J. Virol.* 69: 6400-7 (1995)) discloses the identical VL30 region that can be obtained from the Harvey murine sarcoma virus (HaMSV) leader, and HaMSV is a member of the type C retrovirus family. Based on this, the Examiner alleges that the claimed invention was *prima facie* obvious. Applicants respectfully traverse this rejection.

U.S. Patent No. 5,925,565 discloses a polycistronic vector, including a retroviral vector employing a VL30 sequence acting as an IRES site or an encapsulation region. Berlioz et al (1995) discloses that this VL30 sequence was isolated from the 5' end of the Harvey murine sarcoma virus which is a member of the type C retrovirus family.

The prior art does not disclose a vector, viral particle or cell comprising a nucleotide sequence isolated from the 5' end of the genomic RNA of a REV or MSV virus and methods using thereof. Thus, claims limited to this aspect are inventive over the state of the art.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 1, 2, 8-12, 17-19 and 21-23 under 35 U.S.C. § 103(a).

Claim 17 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Berlioz et al. (*J. Virol.* 69: 6400-7 (1995) in view of Dirks et al. (U.S. Patent No. 6,060,273). Berlioz et al. discloses the construction of a dicistronic MLV-derived retroviral vector, pVL-CBT2, comprising the VL30 sequence of the Harvey murine sarcoma virus leader inserted between phosphatase and neomycin genes. Berlioz et al. further discloses that the 5' VL30 sequence functions as an IRES for efficient translation of the neomycin gene and for packaging of RNA into MLV virions. While acknowledging that Berlioz et al. does not comprise a gene encoding a product selected from Factor VIII, Factor IX, the CFTR protein, dystrophin, insulin, alpha-, beta- and gamma interferon or an interleukin, the Examiner has stated that Dirk et al., however, discloses multicistronic expression units in which the cistrons comprise genes encoding Factor VIII, creatine kinase and hemoglobin.

Based on the teachings of these two publications, the Examiner has concluded that it would have been obvious to a person of ordinary skill in the art at the time of invention to modify a dicistronic MLV-derived retroviral vector of Berlioz et al. by substituting the gene encoding phosphatase with a gene encoding factor VIII as disclosed in Dirk et al.

Dirk et al. discloses multicistronic expression cassettes employing an IRES of viral cellular or synthetic origin to direct the expression of a therapeutic protein, including Factor VIII, Factor IX, the CFTR protein, dystrophin, insulin, alpha, beta or gamma interferon and interleukin. The Examiner has stated that it would have been obvious to modify a polycistronic MLV-derived retroviral vector as described in Berlioz et al. by

substituting the plap gene with one encoding a therapeutic protein as described in Dirk et al.

Limitation of claim 17 to a recombinant vector employing a nucleotide sequence isolated from the 5' end of the genomic RNA of a REV or MSV virus renders the claimed invention patentable over the state of the art.

Therefore, Applicants respectfully request withdrawal of the rejection of claim 17 under 35 U.S.C. § 103(a).

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned agent concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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